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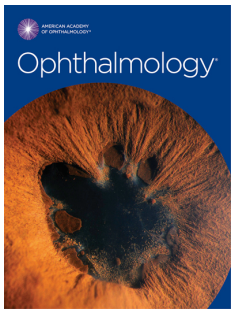

Association between vaccination with the BNT162b2 mRNA COVID-19 vaccine and non-infectious uveitis: a population-based study

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PII: S0161-6420(22)00395-5

DOI: https://doi.org/10.1016/j.ophtha.2022.05.015

Reference: OPHTHA 12071

To appear in: *Ophthalmology*

Received Date: 21 January 2022

Revised Date: 19 May 2022

Accepted Date: 19 May 2022

Please cite this article as: Tomkins-Netzer O, Sar S, Barnett-Griness O, Friedman B, Shyriaieva H, Saliba W, Association between vaccination with the BNT162b2 mRNA COVID-19 vaccine and non-infectious uveitis: a population-based study, *Ophthalmology* (2022), doi: https://doi.org/10.1016/j.ophtha.2022.05.015.

Association between vaccination with the BNT162b2 mRNA COVID-19 vaccine and non-infectious uveitis: a population-based study

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Financial Support: None

Running head: BNT162b2 vaccine and non-infectious uveitis

No conflicting relationship exists for any author

Abstract

Purpose: To assess the association between BNT162b2 mRNA COVID-19 vaccine and the risk of active non-infectious uveitis (NIU).

Design: A retrospective population-based study

Participants: 2,602,557 people who received the first vaccine dose between 20 December 2020 and 30 April 2021, and 2,441,719 who received the second vaccine dose between 10 January 2021 and 30 April 2021.

Methods: Events of active NIU were included if they occurred within 21 days following either vaccine dose. Active NIU was defined as newly active or worsening ocular inflammation requiring initiation or increase in local or systemic corticosteroids. Observed cases were compared to the expected number, based on the experience of the population in 2019.

Main outcome measures: Age-Gender adjusted standardized incidence ratios (SIRs) and attributable risks (ARs) following BNT126b2 vaccination.

Results: Overall, 100 and 88 events of active NIU were recorded within 21 days following the first and the second vaccine dose, respectively. Using the experience of the population in 2019 as reference, after the first dose the estimated age-gender adjusted SIR was 1.41 (95% CI, 1.15-1.71) along with a 21-days attributable risk of 1.12 cases per 100,000 vaccinees. Following the second dose, the SIR was 1.31 (95% CI, 1.05-1.62) with an estimated attributable risk of 0.86 cases per 100,000 vaccinees. Anterior uveitis was the most common site of inflammation, occurring in 90.96% of eyes and idiopathic uveitis was the most common etiology (54.08%).

Conclusions: Our study suggests the BNT162b2 mRNA COVID-19 vaccine might be associated with an increased risk of active NIU. However, considering the small effect size and study limitations this study does not provide proof for cause-and-effect. The small estimated attributable risks suggest that the impact on public health is relatively minor.

Introduction

Prevention and treatment of the COVID-19 pandemic is the leading issue in current global healthcare. The BNT162b2 messenger-RNA vaccine demonstrated high efficacy in preventing SARS-CoV-2 infection, hospitalization and related death.[1–4] Large population-based studies demonstrated the vaccine has a good safety profile, though some increased risk of incident systemic complications was noted, including varicella zoster infection, lymphadenopathy, Guillian-Barre syndrome and myocarditis.[1,4–12]

In many countries two doses of the vaccine and a booster dose are currently recommended for the general population over the age of twelve and two doses for children between the ages of 5-12 years.[9,13]

Previous associations between vaccines and ocular complications have been suggested, including uveitis.[14–16] Following the COVID-19 global vaccination campaign, cases are now reported of possible vaccine-related ocular complications.[17] Most are single or small case reports and include acute macular neuroretinopathy,[17]

central serous retinopathy,[18] corneal graft rejection, [19–21] cranial nerve palsies and particularly incident and relapses of uveitis.[22–24] The majority of uveitis cases are related to anterior uveitis, (though several reports include cases of multiple evanescent white dot syndrome (MEWDS), Vogt-Koyanagi-Harada (VKH) syndrome and idiopathic panuveitis. [10,17,25–32] In all these reports the association to the vaccine is related to temporal proximity and developed between 1-30 days following receiving a vaccine dose. However, it remains unclear whether the vaccine is related to an increase in the incidence of uveitis and whether there are populations at higher risk.

In this study we examined a large population-based database of individuals who received the BNT162b2 vaccine and compared the rates of active non-infectious uveitis (NIU) requiring treatment, both to pre and post COVID-19 rates.

Methods

A retrospective cohort study was conducted using de-identified healthcare records from the Clalit Health Services (CHS) database. CHS is one of four national health maintenance organizations (HMO) in Israel that insure and provide healthcare according to governmental guidelines. It insures >4.7 million people comprising approximately 52% of the population of Israel and is representative of the entire population at large. CHS information systems are fully digitized and generated from both outpatient facilities and all national hospitals including records of primary care physicians, community specialty clinics, hospitalizations, laboratories, and pharmacies. Information regarding COVID-19 infections and vaccinations are collected centrally. The study was approved by the CHS institutional review board (#CMC-022-21) and was exempt from the requirement for informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Study Design

We performed a retrospective cohort study with a non-concurrent historic comparative group. In this approach the observed cases of active NIU appearing after COVID-19 vaccination were compared to the expected cases of active NIU as estimated based on the experience of the CHS population during two periods; i) 2019 prior to COVID-19 pandemic and vaccine introduction in Israel, ii) 2020 during the COVID-19 pandemic but before introduction of the vaccine.

Study Population

The study included all patients who received at least one dose of the BNT162b2 vaccine. To estimate the observed cases of NIU after the first vaccine dose, we identified all CHS members aged ≥16 years who received the first dose of the vaccine starting from 20 December 2020, the start date of the mass COVID-19 vaccination campaign in Israel, till 30 April 2021. Identified subjects constituted the population for the estimation of the standardized incidence ratio (SIR) of active NIU after the first vaccine dose. Among them, those who received the second vaccine dose by 30 April 2021 constituted the population for the estimation of SIR after the second vaccine dose. The first historic comparative group included the CHS members aged ≥16 on January 1, 2019 and the second comparative historic group included CHS members aged ≥16 on September 1, 2020.

Events were defined as suspected for active NIU if a medical record documented a diagnosis of NIU, according to international classification of disease ninth revision (ICD-9) definitions (Table S1) with a concomitant prescription of topical, regional or systemic corticosteroids (Table S2). All case records meeting this definition were then reviewed by an investigator (OTN). Suspected events were confirmed and thus included in the study as active NIU if in the case review an ophthalmic examination by an ophthalmologist documented newly active or worsening inflammation (according to the standardization of uveitis nomenclature criteria)[33] and local or systemic corticosteroids were initiated or increased. Otherwise, suspected events were excluded if not documented by an ophthalmologist, a full ophthalmic

examination was not performed, no signs of active inflammation were documented, the patient had documented medical history of any infectious uveitis (including herpetic uveitis or toxoplasmosis) or if local or systemic corticosteroids were not initiated or increased. Following the manual review, we rejected 38.38% of cases from the 2019 reference population, 37.59% from the 2020 reference population and 38.82% from those who received the vaccine. The main reasons for case rejection were no documented evidence of signs of active uveitis, an infectious uveitis diagnosis or misdiagnosis of uveitis. Vaccine-related events were recoded if they occurred during a 21-day window following either the first or second BNT162b2 vaccine dose. A 21-day windows was chosen because according to local guidelines the second dose was administered 21 days following the first dose. For the 2019 historic reference population (pre-COVID-19 period), events were recorded if they occurred during a matched observation period in 2019 (Jan-May). Whereas for the 2020 reference population (post-COVID-19, and pre-vaccination period), events were recorded if they occurred between 1 September 2020 and 18 December 2020 (before vaccination). For the 2020 reference population the period was chosen to account for changes in patient healthcare behavior during the first months of the pandemic. For all people identified, only the first event of active NIU during the follow-up period was included. If a second event was recorded following the second dose it was considered a continuation of the first event. A record review of previous diagnoses of uveitis since 1 January 1999 was conducted, to identify all individuals with previously known NIU (Table S1).

Additional variables were recorded for the vaccine-related events, including time (days) following vaccination, anatomical site of inflammation, best corrected visual

acuity (BCVA) and uveitis definition according to ICD-9. BCVA was converted to logarithm of the minimum angle of resolution (logMAR). For BCVA of counting fingers or worse, the following conversion was used: counting fingers 2.0 logMAR; hand movements 2.3 logMAR; light perception 2.6 logMAR; and no light perception 2.9 logMAR.[34]

Statistical methods

The observed number of cases of active NIU occurring within 21 days after each vaccine dose (first and second) were compared to the expected number of cases, based on estimation from historic data. Observed cases after the first vaccine dose were assessed in those who received the first dose between 20 December 2020 and 30 April 2021, and the observed cases after the second vaccine dose were assessed in those who received the second dose between 10 January 2021 and 30 April 2021. Both cohorts were retrospectively followed for 21 days for active NIU ascertainment. The expected incidence rate of active NIU was estimated based on the experience of the CHS population in 2019 during the same period (January-May) and in 2020 between 1 September and 18 December. We used the same criteria for identifying cases among these reference populations as those for the cases following vaccination. These rates were applied to estimate the number of active NIU cases that were expected to occur within 21 days after each of the first and the second vaccine dose. Standardized incidence ratios (SIRs) were computed by dividing the observed by the expected number of active NIU cases for each vaccine dose, for each gender, for age groups 16-44, 45-64, and ≥65 years as well as for the total

population (adjusted for gender and age) along with the 95% Poisson-based confidence intervals (using the STDRATE procedure in the SAS© Software). We calculated the attributable risk fraction among vaccinated as (SIR-1)/SIR, and the attributable risk (AR) for 100,000 vaccinees was calculated by multiplying the risk after each vaccine dose by the ARF. Cumulative incidence by time from vaccine dose (1st and 2nd separately) was estimated using the Kaplan-Meier method.

Subgroup analysis by past history of uveitis (No/Yes) was performed. To calculate the SIRs for the first and second vaccine dose among subjects with previous history of NIU we used as reference the 2019 and 2020 populations with previous history of NIU. Similarly, for subjects with no history of NIU, the reference populations were the 2019 and 2020 populations with no history of NIU. In the subgroup analysis we conducted only age and sex adjusted estimates, because the number of cases in each age group was small.

A Statistically significant SIR was determined when its 95% confidence interval entirely excluded the value 1. No adjustment for multiple comparisons was performed. All analyses were performed using the SAS© software.

Results

Overall, 2,602,557 people with an average age of 46.8 ± 19.6 years (51.5% females) received the first dose of BNT162b2 mRNA COVID-19 vaccine between 20 December 2020 and 30 April 2021. Of them 2,441,719 received the second vaccine dose between 10 January 2021 and 30 April 2021. A previous diagnosis of NIU was

documented for 18,236 people (0.7%) who received the first dose and 17,250 people (0.7%) who received the second dose (Table S3).

NIU after vaccination

Following vaccination 188 people had confirmed event of active NIU that met the inclusion and exclusion criteria, of them 100 people had event during the 21 days following the first dose and 88 people during the 21 days after the second dose, reflecting a 21-day overall risk of 3.85 and 3.61 per 100,000 vaccinated individuals, respectively (Table 1). The cumulative incidence of active NIU by time from vaccination is presented in Figure 1 for each of the doses. Among those individuals who experienced the event, the median time to active NIU was 8.5 days (interquartile range, IQR 3-16) following the first dose and 10 days (IQR 6.5-15) after the second dose, with 68 (68.0%) and 59 events (67.0%) occurring during the first 14 days following the first and second doses, respectively.

Comparison with historical cohorts

Total time (Person years) at risk and incidence rates for people following vaccination and for the reference populations in 2019 and 2020 are shown in Table 2. The overall incidence rate of active NIU was 66.8 per 100,000 person-years after the first dose and 62.7 per 100,000 person-years after the second vaccine dose. The corresponding rate in the reference populations was 45.7 per 100,000 person-years in 2019, and 45.1 per 100,000 person-years in 2020 (Table 2).

Using the experience of the population in 2019 as reference, the age and gender adjusted SIRs were 1.41 (95% CI, 1.15-1.71) and 1.31 (95% CI, 1.05-1.62) following the first and the second dose, respectively (Table 1). This accounted for an attributable risk (AR) of 1.12 events per 100,000 vaccinees following the first dose and 0.86 events per 100,000 vaccinees following the second dose. Stratified analysis by gender and age revealed that following the first dose the age adjusted SIRs were 1.48 (95% CI, 1.08-1.98) for males and 1.35 (95% CI, 1.02-1.76) for females, resulting in an AR of 1.16 and 1.07 per 100,000 vaccinees, respectively. Following the second dose, the age adjusted SIR among males was 1.46 (95% CI, 1.06-1.98) with an AR of 1.13 events per 100,000 vaccinees. Among females following the second dose the age adjusted SIR was 1.20 (95%CI=0.88-1.60). Similar results were found when 2020 was used as reference population (Table S4).

<u>Subgroup analysis by past history of Uveitis</u>

Table S5 shows the total time (Person years) at risk and incidence rates following vaccination with each dose, and for the reference populations 2019 and 2020, stratified by previous history of uveitis (people without a history of uveitis versus people with previously known uveitis).

Among people without a history of uveitis, the overall risk of new-onset NIU was 1.63 and 1.98 events per 100,000 vaccinated individuals, following the first and the second vaccine dose, respectively (Table 3). Compared with the reference 2019 population with no history of uveitis the age-gender adjusted SIRs for new-onset NIU were 1.3 (95% CI, 0.94-1.76) and 1.57 (95% CI, 1.16-2.08), following the first and the

second vaccine dose, respectively. The corresponding ARs were 0.38 and 0.72 events per 100,000 vaccinees (Table 3). Our data shows that people with a history of uveitis have a high risk of recurrent active NIU event during the observation period (Table 3). Following the first dose the age-gender adjusted SIR for NIU relapse was 1.58 (95% CI, 1.20-2.04), which accounted for an AR of 116.94 per 100,000 vaccinees. Following the second dose the age-gender adjusted SIR for NIU relapse was 1.16 (95% CI, 0.83-1.57), which accounted for an AR of 31.27 per 100,000 vaccinees (Table 3). The results of subgroup analysis using 2020 as reference population were comparable to the analysis using the 2019 reference population (Table S6).

Among uveitis patients with no history of uveitis, the median (IQR) time to active NIU was 8.5 (6 to 18) days and 11 (5.5 to 16), after the 1st vaccine dose (N=42) and the second vaccine dose (N=48), respectively. Among patients with a history of uveitis, the median (IQR) time to active NIU was 8.5 (3 to 15) days and 10 (6.5 to 15), after the 1st vaccine dose (N=58) and the second vaccine dose (N=40), respectively.

<u>Clinical characteristics of active NIU after vaccination</u>

Overall, events of active NIU involved 188 people, of which 166 were unilateral (88.3%, Table 4), with 76 involving the right eye (45.78%), and 22 were bilateral (11.7%). Anterior uveitis was the most common site of inflammation occurring in 171 eyes (90.96%). Average BCVA at time of event was 0.3±0.44logMAR. Clinical investigations were complete for 127 events (67.55%) with idiopathic uveitis the most common etiology (n=106, 56.38%), followed by patients with HLA-B27 associated uveitis (n=12, 6.38%) and Behçet disease (n=2, 1.06%).

Discussion

The introduction of the BNT162b2 mRNA COVID-19 vaccine was a turning point in managing the COVID-19 pandemic. The vaccine is highly effective in preventing severe SARS-CoV-2 infection, hospitalizations and reduces morbidity rates.[1–4] Concerns regarding possible systemic adverse effects of the vaccine were raised, including ocular morbidity. Clinical trials and population-based studies that examined the incidence rates of systemic adverse effects demonstrated an increased risk of some complications, particularly myocarditis among young males, but no increased risk of uveitis was found.[1,8]

Previous reports relate vaccines to events of uveitis, most commonly vaccines for the hepatitis B virus, human papillomavirus and influenza virus.[16,35–37] Reports were mainly of anterior uveitis, but other cases included acute posterior multifocal placoid pigment epitheliopathy, VKH or MEWDS.[14,38–42]

Currently, reports suggest correlations between the BNT162b2 mRNA COVID-19 vaccine and cases of new onset or relapse of uveitis, ranging from re-activations of herpes-related uveitis to new episodes on non-infectious uveitis. In most of these reports the correlation to the vaccine is based only on its occurrence within 30 days after vaccination. [10,17,25,26] The current global vaccination initiative includes large populations receiving a single vaccine over a short period of time, creating a unique

opportunity to address the question of correlations between the vaccine and uveitis. Interestingly, a large population-based study using the same CHS database failed to show an increase in uveitis incidence following the BNT162b2 vaccination.[8] Despite the disparities in the findings of the two studies the results are not contradictory. Differences between the studies in population size, definition of active uveitis and inclusion of people with a previous history of uveitis, suggest the populations and results are not comparable. In our study we took particular care to identify events of active NIU, by manually examining each case and confirming an ophthalmologist reported signs of active inflammation. Our results suggest that for the general population there may be an association between the incidence of active NIU and the BNT162b2 vaccine compared to 2019 and 2020, with a small attributable risk. This risk is outweighed by the impact of the vaccine on reducing the significant morbidity and mortality posed by the COVID-19 infection.

Possible associations between vaccines and uveitis are of particular interest to ophthalmologists and patients with known uveitis. Many patients with NIU are treated with immunosuppression drugs and have concerns regarding the efficacy of the vaccine and potential disease reactivation. Our results suggest that among patients with a history of uveitis there was an increased incidence of active NIU, accounting for an overall AR of approximately one case per 1,000 vaccinated people, and up to 3 cases per 1000 vaccinated people in certain age groups. Over 90% of cases were anterior uveitis and treated topically. Studies examined patients with other systemic autoimmune diseases including rheumatoid arthritis and systemic

lupus erythematosus also demonstrated few cases of disease relapse. [43–46] Ophthalmologists should be aware of this potential increased risk of relapse to patients with a history of uveitis and counsel them to be vigilant during the weeks following vaccination.

While our results suggest an increased risk of uveitis among certain patient populations, it is important to address the overall excess morbidity that can be attributed to the vaccine. Based on evidence gained this far, the impact of this additional morbidity is outweighed by the reduced systemic COVID-19 morbidity achieved through vaccination. Similar to other reports, the results of this study do not support preventing vaccination from patients,[6,8,47] but they should be advised of the symptoms of active uveitis, particularly during the first 14 days following each dose and recommended to seek immediate ophthalmic care if they occur.

In this study we chose to examine the incidence of active NIU during the first 21 days following each of the first two doses. This time window is deemed to be sufficient for short-term complications, without being too long to dilute the effect, and is in line with the time window used by several studies to examine short-term complications of COVID-19 vaccine.[6,8] This timeframe limits the effect of other potential factors that could lead to active disease, unrelated to the vaccine. Other studies on vaccines used longer timeframes, which increases the chance of other unrelated factors influencing new cases. [25]

Our study has several limitations related to its retrospective observational nature and having relied on data originally collected for purpose of administrative and clinical management and not specifically designed for the current study. As such, data extraction in our study might be subject to errors and lack of data, most likely leading to nondifferential misclassification. In order to identify events of active uveitis we included only patients seen by an ophthalmologist. While this might result in loss of some cases, in Israel there is good access to ophthalmologists and the majority of patients with ocular complaints would not be treated general practitioners. Cases with a diagnosis of uveitis related to an infectious cause were excluded from this study, but some incident acute cases did not complete their systemic investigations and we cannot exclude that some might represent uveitis due to an infective cause. Additionally, our cohort had a relatively large group with a previous diagnosis of uveitis (0.7%), which would include patients with single events of ocular inflammation and not treated and followed regularly by ophthalmologists. However, we tried to minimize this misclassification by manually reviewing all cases and only including events of active uveitis with no known infective cause. Furthermore, this study examined only the risk of developing active uveitis and we were unable to follow patients and ascertain their final clinical and visual outcome following treatment for uveitis. Another potential limitation is surveillance bias due to differences in terms of seeking medical care. However, generally active uveitis is symptomatic and therefore it is unlikely that a patient is not seen by a physician, regardless of vaccination status, hence we assume that the influence of this bias is minimal. Although our large sample size allowed us to conduct stratified analysis, adjustment was limited only to age and gender. Hence, residual confounding

remains a major concern of the current study, as we did not control for other risk factors for NIU that might differ between vaccinated subjects and the general population. Based on the limitations inherent in the study design, this study should be considered as a signal detection hypothesis generating study. Furthermore, it is important to note that causality involves much more than temporal association. Considering the small effect size and the inherent limitations, our study does not provide a proof for cause and effect. Further studies are needed to examine this association and determine the visual burden of this excess morbidity.

In conclusion, our study suggests that the BNT162b2 mRNA COVID-19 vaccine might be associated with increased risk of NIU. The small estimated attributable risks suggest that the impact on public health is relatively minor. However, considering the small effect size and study limitations this study does not provide proof for cause-and-effect. Future studies are needed to explore the association. The benefits of vaccination outweigh the possible link to active uveitis and support the continued use of the vaccine, while patients with known uveitis should be aware of symptoms of relapse.

375 Figure Legends

376 Figure 1- Cumulative incidence of active non-infectious uveitis, by dose.

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Table 1- Standardized incidence ratios of active non-infectious uveitis after 1st or 2nd vaccine dose, stratified by gender and age groups, using 2019 as reference population

1st Dose

Gender	Age group, yrs	Vaccinees, n	Observed Events, n	Risk (per 100,000 vaccinees)	Expected Events, n	SIR and 95% CI	AR per 100,000 vaccinees
All	**Age-gender adjusted**	**2602557**	**100**	**3.85**	**70.97**	**1.41 [1.15-1.71]**	**1.12**
Males	16-44	655658	21	3.21	9.48	2.22 [1.37-3.39]	1.76
	45-64	341289	5	1.47	11.44	0.44 [0.14-1.02]	-1.89
	65+	264191	19	7.20	9.45	2.01 [1.21-3.14]	3.62
	Age adjusted	**1261138**	**45**	**3.57**	**30.36**	**1.48 [1.08-1.98]**	**1.16**
Females	16-44	661032	10	1.51	11.64	0.86 [0.41-1.58]	-0.25
	45-64	355666	18	5.06	13.64	1.32 [0.78-2.09]	1.23
	65+	324721	27	8.32	15.34	1.76 [1.16-2.56]	3.59
	Age adjusted	**1341419**	**55**	**4.10**	**40.61**	**1.35 [1.02-1.76]**	**1.07**

2nd Dose

Gender	Age group, yrs	Vaccinees, n	Observed Events, n	Risk (per 100,000 vaccinees)	Expected Events, n	SIR and 95% CI	AR per 100,000 vaccinees
All	**Age-gender adjusted**	**2441719**	**88**	**3.61**	**67.10**	**1.31 [1.05-1.62]**	**0.86**
Males	16-44	603921	7	1.16	8.73	0.80 [0.32-1.65]	-0.29
	45-64	323337	26	8.05	10.83	2.40 [1.57-3.52]	4.69
	65+	254712	9	3.54	9.11	0.99 [0.45-1.88]	-0.04
	Age adjusted	**1181970**	**42**	**3.56**	**28.67**	**1.46 [1.06-1.98]**	**1.13**
Females	16-44	610436	18	2.95	10.74	1.68 [0.99-2.65]	1.19
	45-64	336112	16	4.76	12.89	1.24 [0.71-2.02]	0.93
	65+	313201	12	3.83	14.79	0.81 [0.42-1.42]	-0.89
	Age adjusted	**1259749**	**46**	**3.65**	**38.43**	**1.20 [0.88-1.60]**	**0.60**

SIR- Standardized incidence ratio; AR- attributable risk

Table 2 - Incidence rates of active non-infectious uveitis after the 1st and 2nd vaccine dose, and in reference populations (2019 and 2020)

		2019 - Reference			2020 - Reference			First vaccine dose (within 21 days after)			Second vaccine dose (within 21 days after)		
Gender	**age group, yrs**	**Person years**	**Events**	**Incidence Rate (per 100,000 P-Y)**	**Person years**	**Events**	**Incidence Rate (per 100,000 P-Y)**	**Person years**	**Events**	**Incidence Rate (per 100,000 P-Y)**	**Person years**	**Events**	**Incidence Rate (per 100,000 P-Y)**
All	**16-44**	720499	201	27.9	527533	162	30.7	75702	31	41.0	69819	25	35.8
	45-64	330499	207	62.6	242573	128	52.8	40071	23	57.4	37914	42	110.8
	65+	260218	191	73.4	194265	145	74.6	33858	46	135.9	32651	21	64.3
	Total	**1311216**	**599**	**45.7**	**964372**	**435**	**45.1**	**149631**	**100**	**66.8**	**140384**	**88**	**62.7**
Female	**16-44**	362576	111	30.6	265541	95	35.8	38006	10	26.3	35096	18	51.3
	45-64	170940	114	66.7	124661	77	61.8	20448	18	88.0	19324	16	82.8
	65+	146055	120	82.2	108885	89	81.7	18669	27	144.6	18007	12	66.6
	Total	**679571**	**345**	**50.8**	**499088**	**261**	**52.3**	**77123**	**55**	**71.3**	**72428**	**46**	**63.5**
Male	**16-44**	357923	90	25.1	261992	67	25.6	37696	21	55.7	34722	7	20.2
	45-64	159559	93	58.3	117912	51	43.3	19622	5	25.5	18589	26	139.9
	65+	114163	71	62.2	85380	56	65.6	15189	19	125.1	14644	9	61.5
	Total	**631645**	**254**	**40.2**	**465284**	**174**	**37.4**	**72508**	**45**	**62.1**	**67956**	**42**	**61.8**

Table 3- Adjusted Standardized incidence ratios of active non-infectious uveitis, after 1st or 2nd vaccine dose, stratified by past history of uveitis, using 2019 as reference population

1st Dose

Past history of NIU	Gender	Adjustment	Vaccinees, n	Observed Events, n	Risk (per 100,000 vaccinees)	Expected Events, n	SIR and 95% CI	AR per 100,000 vaccinees
No	**All**	**Age-gender adjusted**	**2584321**	**42**	**1.63**	**32.31**	**1.30 [0.94-1.76]**	**0.38**
	Males	Age adjusted	1252498	21	1.68	14.22	1.48 [0.91-2.26]	0.54
	Females	Age adjusted	1331823	21	1.58	18.09	1.16 [0.72-1.77]	0.22
Yes	**All**	**Age-gender adjusted**	**18236**	**58**	**318.87**	**36.73**	**1.58 [1.20-2.04]**	**116.94**
	Males	Age adjusted	8640	24	278.39	15.12	1.59 [1.02-2.36]	103.03
	Females	Age adjusted	9596	34	355.33	21.61	1.57 [1.09-2.20]	129.48

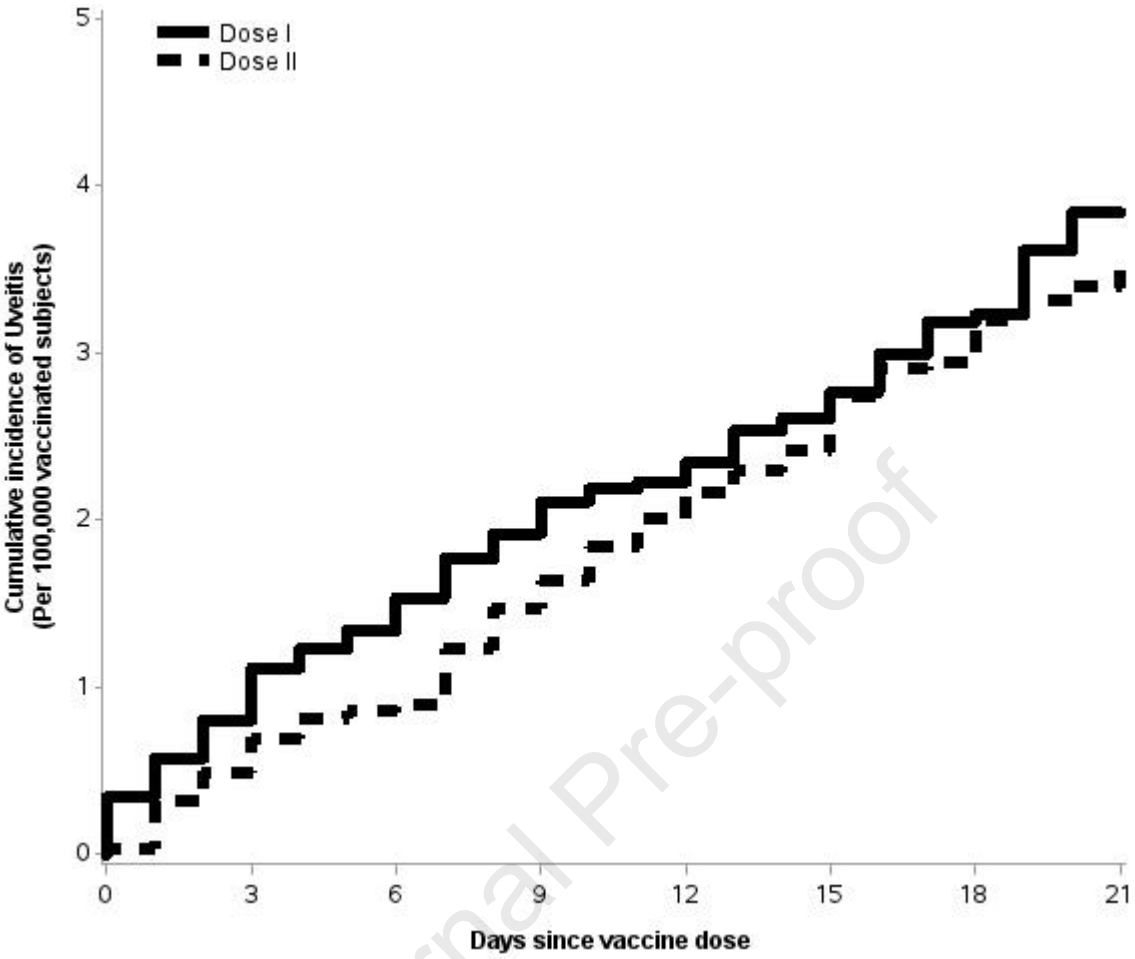
2nd Dose

Past history of NIU	Gender	Adjustment	Vaccinees, n	Observed Events, n	Risk (per 100,000 vaccinees)	Expected Events, n	SIR and 95% CI	AR per 100,000 vaccinees
No	**All**	**Age-gender adjusted**	**2424469**	**48**	**1.98**	**30.61**	**1.57 [1.16-2.08]**	**0.72**
	Males	Age adjusted	1173811	25	2.13	13.45	1.86 [1.20-2.74]	0.98
	Females	Age adjusted	1250658	23	1.84	17.16	1.34 [0.85-2.01]	0.47
Yes	**All**	**Age-gender adjusted**	**17250**	**40**	**232.32**	**34.62**	**1.16 [0.83-1.57]**	**31.27**
	Males	Age adjusted	8159	17	208.68	14.24	1.19 [0.70-1.91]	33.92
	Females	Age adjusted	9091	23	253.55	20.38	1.13 [0.72-1.69]	28.88

NIU- non -infectious uveitis; SIR- Standardized incidence ratio; AR- attributable risk

Table 4- Clinical characteristics of active non-infectious uveitis cases following BNT162b2 mRNA COVID-19 vaccine

	N (%)
Unilateral disease	166 (88.3)
Right eye	76 (45.78)
Anatomical site	
Anterior Uveitis	171 (90.96)
Intermediate Uveitis	9 (4.79)
Posterior Uvetiis	1 (0.53)
Pan Uveitis	7 (3.72)
Etiology	
Idiopathic	106 (56.38)
HLA B27	12 (6.38)
Behçet disease	2 (1.06)
Fuchs heterochromic iridocyclitis	2 (1.06)
Multifocal choroiditis	2 (1.06)
Posner Schlossman syndrome	1 (0.53)
BCVA, LogMAR, mean±SD	0.3±0.44



Précis

The BNT162b2 vaccine might be associated with an increase in the incidence of active non-infectious uveitis during the first 21 days after vaccination. However, the effect size is small and does not support a cause and effect.